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Minireview

Molecules and Cells

A Time to Fast, a Time to Feast: The Crosstalk between Metabolism and the Circadian Clock

Judit Kovac[1,3], Jana Husse[2,3], and Henrik Oster[1,*]

The cyclic environmental conditions brought about by the 24 h rotation of the earth have allowed the evolution of endogenous circadian clocks that control the temporal alignment of behaviour and physiology, including the uptake and processing of nutrients. Both metabolic and circadian regulatory systems are built upon a complex feedback network connecting centres of the central nervous system and different peripheral tissues. Emerging evidence suggests that circadian clock function is closely linked to metabolic homeostasis and that rhythm disruption can contribute to the development of metabolic disease. At the same time, metabolic processes feed back into the circadian clock, affecting clock gene expression and timing of behaviour. In this review, we summarize the experimental evidence for this bimodal interaction, with a focus on the molecular mechanisms mediating this exchange, and outline the implications for clock-based and metabolic diseases.

INTRODUCTION

The adaptation to environmental changes brought about by the succession of day and night offers strong advantages for the efficient usage of natural resources and, hence, is a major evolutionary selection criterion (Pittendrigh, 1993). Not surprisingly, all but the simplest species living on Earth have evolved time-keeping mechanisms that enable them to predict and adapt to upcoming time-dependent events (Harmer et al., 2001). These internal clocks, termed circadian from Latin “circa diem” meaning “about a day”, are a remarkable example of parallel evolution that emphasizes the importance of temporal resolution for living organisms. Circadian clocks anticipate daily events and adapt behaviour and physiology in an attempt to minimise energy expenditure and maximise the chance of survival.

Circadian regulation does not only serve the alignment of internal and external rhythms, but also provides a powerful means to achieve temporal compartmentalisation at both inter- and intracellular levels (Takahashi et al., 2008). According to the current model, mammalian circadian clocks are based on cellular oscillators built from a set of clock genes organised in interlocked transcriptional feedback loops. The transcription factors CLOCK (or, in some tissues, NPAS2) and BMAL1 (ARNTL) drive expression of two *Cry* and three *Per* genes, as well as hundreds of so called *clock controlled genes* (CCGs) via E-box mediated regulation. PER and CRY proteins negatively feed-back on CLOCK/BMAL1 activity, thereby generating a stable 24 hr rhythm of transcriptional activity. Several accessory feedback loops - one of them involving the nuclear hormone receptors *Rev-erbα* (*Nr1d1*) and *Rorα* (*Rora*) - stabilise this rhythm and provide further means for in- and output to and from the molecular clock (Ko and Takahashi, 2006). The nature of CCGs varies between different tissues, providing a way to translate time information into physiologically meaningful signals (Duffield, 2003).

In mammals, a master circadian pacemaker is located in the hypothalamic suprachiasmatic nuclei (SCN). From the SCN peripheral clocks throughout the rest of the body are synchronised with each other and with external time. The synchronisation mechanisms of the circadian timing system have not yet been fully understood, but likely involve humoral, neuronal as well as indirect pathways such as the activity-mediated regulation of food intake and body temperature (Stratmann and Schibler, 2006). The major synchroniser (or *Zeitgeber*) of circadian rhythms is light. Light information reaches the SCN from visual and non-visual photoreceptors in the retina via the retino-hypothalamic tract and results in the release of glutamate at SCN synapses (Foster and Hankins, 2007). Other *Zeitgeber* exist, but their signalling mechanisms are poorly studied. Some of them involve other brain nuclei and, most likely, other (peripheral) clocks. A striking example for this is the entrainment of peripheral oscillators by metabolic signals. Independently of the SCN, the temporal restriction of food access can rapidly reset clock gene rhythms in many tissues such as the liver or the kidney (Damiola et al., 2000). Similarly, light has been shown to directly affect clocks in the adrenal cortex and the secretion of endocrine factors such as glucocorticoids from this gland (Ishida et al., 2005; Oster et al., 2006). It is likely that other time cues will affect different oscillators and provide additional input for the entrainment of the circadian timing system.

While food restriction uncouples SCN and peripheral clocks, there is also feedback from the periphery to the master pacemaker. This includes arousal-associated circuits and hormone-sensitive brain areas such as the raphe or the arcuate nuclei

[1]Circadian Rhythms Group, Max Planck Institute of Biophysical Chemistry, 37077 Göttingen, Germany, [2]Genes and Behaviour Department, Max Planck Institute of Biophysical Chemistry, 37077 Göttingen, Germany, [3]These authors contributed equally to this work.
*Correspondence: henrik.oster@mpibpc.mpg.de

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that themselves project to the SCN (Buijs et al., 2006). A direct neuronal feedback, e.g. from the autonomic nervous system, is likely, but experimental evidence for this is still missing. The optimisation of energy expenditure is one of the main functions of circadian timekeeping (see above). Thus, efficient interactivity of the circadian and metabolic regulatory centres is crucial for optimal environmental adaptation. The molecular aspects of this cross-talk and its (patho-) physiological implications are summarised below.

Circadian control of metabolism

A major function of the circadian system is the regulation of the metabolic machinery in preparation for temporal variations in the abundance of nutrients. Not surprisingly, various humoral factors associated with metabolic control show diurnal rhythms of concentration such as glucose, fatty acids and triglycerides, but also glucocorticoids, insulin and catecholamines. By these means clock-regulated anticipation of external events optimizes physiological energy expenditure and, hence, increases general fitness (Bray and Young, 2007).

In humans, clock-related metabolic regulation is tightly linked to the regulation of sleep. The circadian clock regulates the sleep/wake cycle by synchronising phases of sleepiness and arousal throughout the day. In addition, a homeostatic component of unknown anatomical origin regulates the "need for sleep" in response to prolonged wakefulness. Recent work suggests that both processes are not entirely separated and clock genes may affect both circadian and homeostatic circuits (Mistlberger, 2005). Changes in human lifestyle - most prominently observed during the last decades - have led to a striking decrease in average sleep duration in most industrial countries, correlated with a dramatic increase in the prevalence of metabolic disorders (Laposky et al., 2008). Acute sleep restriction in healthy subjects promotes increased appetite, reduced leptin secretion, elevated ghrelin levels, and increased glucose resistance (Spiegel et al., 1999; 2004). Likewise, shift workers show higher metabolic risk factors for the development of obesity, diabetes type II, metabolic syndrome and cardio-vascular disease (Bray and Young, 2007). All these attributes are under circadian control, indicating that metabolic phenotypes might be the consequence of a misalignment between circadian clocks and physiology (Shea et al., 2005). Genetic variations in human circadian clock genes have been associated with metabolic phenotypes. Haplotype analyses revealed that *CLOCK* gene polymorphisms are correlated with the development of metabolic syndrome, while certain *BMAL1* alleles are linked to type II diabetes and hypertension (Scott et al., 2007; Woon et al., 2007). These data propose that the transcription factors of the positive limb of the circadian clock may serve a protective role in the incidence of metabolic diseases.

Indications for a causal relationship between the circadian clock and metabolic regulation have been documented in circadian clock mutant mice (see Table 1). The dominant negative *Clock* mutant shows irregular locomotor activity and food intake behaviour. *Clock* animals develop obesity combined with increased levels of cholesterol, triglycerides, glucose and leptin, and a decrease in insulin secretion (Turek et al., 2005). Additionally, these mice absorb more lipids and carbohydrates than peptides via the intestine, most likely due to a lack of cyclic nutrient transport proteins (Pan and Hussain, 2009). Both, *Clock* mutant and *Bmal1* deficient mice show impaired gluconeogenesis, glucose tolerance and insulin sensitivity (Rudic et al., 2004). In liver-specific *Bmal1* deficient animals, defects in glucose balance are reflected by a loss of rhythmicity in the expression of genes important for glucose mobilisation such as glucose-6-phosphate translocase (*Slc37a4*), phosphoenolpyruvate carboxykinase 2 (*Pck2*), adenylate kinase 4 (*Ak3l1*) and glucose transporter 2 (*Slc2a2*) (Lamia et al., 2008). Similar to *Clock* mutant mice, *Per2* deficient animals consume more food during their normal rest phase and develop obesity when fed on a high fat diet. Interestingly, this phenotype can be restored after intraperitoneal application of the melanocyte stimulating hormone α-MSH, involved in the regulation of appetite (Yang et al., 2009). Increased serum levels of very low density lipoproteins (VLDLs) and apolipoprotein C-III were found in mice lacking *Rev-erb*α (Raspe et al., 2002).

Peripheral clocks regulate cell and tissue physiology via the rhythmic activation of hundreds of CCGs in a tissue-specific manner (Fig. 1). Transcriptome studies in metabolically relevant peripheral tissues such as liver, adipocytes, pancreas and the heart highlight the importance of CCGs in the regulation of numerous metabolic processes (Laposky et al., 2008). It seems that many key regulatory elements of energy conversion pathways, such as glucose and lipid metabolism, mediate metabolic alignment with external time. In cultured adipocytes, BMAL1 controls adipogenesis via the induction of *PPAR*γ, *AP2* (*FABP4*), sterol regulatory element binding protein 1 (*SREBP-1*) and CCAAT/enhancer binding proteins (*C/EBPs*) (Shimba et al., 2005). Defects in adipocyte differentiation were also seen in the absence of REV-ERBα, an upstream regulator of *Bmal1* transcription (Wang and Lazar, 2008). Additionally, REV-ERBα represses lipid metabolism by binding to an AGGTAC motif in the promoter region of *ApoC-III* (Raspe et al., 2002). In skeletal muscle, RORα regulates lipid homeostasis via direct activation of carnitine palmitoyltransferase 1 (*CPT1*), involved in fatty acid oxidation, and caveolin-3 (Lau et al., 2004). Rhythmic transcriptional activation by CLOCK/BMAL1 is a key regulator of lipid metabolic enzymes such as acyl-CoA oxidase (*AOX*), 3-hydroxy-3-methylglutaryl coenzyme A (*HMG-CoA*) synthase (*Hmgcs1*) and cellular retinol binding protein II (*CRBP II*) (Inoue et al., 2005).

Circadian regulation of metabolism is not limited to peripheral clocks, but at the same time involves functional modulation of metabolic control centres in the brain. Rhythmic clock gene expression has not only been shown in the SCN, but in many other brain regions. These include the forebrain nuclei proximal to the third ventricle that express orexigenic (NPY, AgRP) and anorexigenic (POMC, CART) neuropeptides, as well as the dorsomedial nucleus and orexin-expressing neurons of the lateral hypothalamus (Green et al., 2008). Both regions serve as relay sites to arousal- and feeding-regulatory centres in the brainstem and the basal hypothalamus, respectively. *Clock* gene function itself is essential for normal regulation of ghrelin, CART and orexin levels in the hypothalamus (Turek et al., 2005). Thus, the appropriate integration of central and peripheral metabolic circadian regulation seems essential for the fine-tuning of overall metabolic homeostasis.

A possible risk factor for cardiovascular disease is a circadian dysfunction of the heart, where CLOCK regulates myocardial oleate oxidation and oxygen consumption by activation of fatty acid transport protein 1 (*Slc27a1*) as well as of the a3 and b3 subunits of NADH hydrogenase (*Ndufa3/b3*) (Bray et al., 2008). Furthermore, metabolic processes unrelated to energy balance have been reported to be regulated by the circadian clock. BMAL1 target genes are involved in xenobiotic detoxification and the conversion of reactive oxygen species (ROS) which are prime candidates for causing age-related degenerative processes (Kondratov et al., 2006). PER2, on the other hand, has a protective role in the susceptibility to alcohol and the

Table 1. Mediators of circadian clock metabolism interaction

Factor	Tissue	Function	Targets	References
Clock genes				
Bmal1	Liver Adipocytes	Glucose mobilisation Adipogenesis	*Slc37a4*, *Pck2*, *Ak3l1*, *Slc2a2* *Pparg2*, *Ap2*, *Srebp-1*, *C/EBPs*	Lamia et al. (2008) Shimba et al. (2005)
Clock	Hypothalamus Heart	Appetite regulation Oleate oxidation Oxygen consumption	*Orexin*, *Ghrelin*, *Cart* *Slc27a1* *Ndufa3/b3*	Turek et al. (2005) Bray et al. (2008)
Per2	Hypothalamus	Appetite regulation	α-MSH	Yang et al. (2009)
Rev-erbα	Adipose tissue Liver, serum, kidney	Adipocyte differentiation Triglyceride catabolism	*Pparg2* *APOC-III*, VLDL triglycerides	Wang and Lazar (2008) Raspe et al. (2002)
Rorα	Skeletal muscle	Fatty acid oxidation	*Cpt1*, *Caveolin-3*	Lau et al. (2004)
Metabolic sensors				
Ppara	Liver	Lipid and energy metabolism	*Bmal1*, REV-ERBα	Canaple et al. (2006); Gervois et al. (1999)
Pparg	Adipose tissue	Adipocyte differentiation	REV-ERBα	Fontaine et al. (2003)
Pgc-1α	Liver, skeletal muscle	Gluconeogenesis and energy metabolism	*Bmal1*, REV-ERBα	Liu et al. (2007)
Sirt1, *Nampt*, redox state	Liver, mouse embryonic fibroblasts	Cellular metabolism	CLOCK (NPAS2) /BMAL1-mediated transcription	Nakahata et al. (2009); Ramsey et al. (2009); Rutter et al. (2001)
CO, heme	Liver, HeLa cells	Oxidative metabolism	REV-ERBα, NPAS2	Dioum et al. (2002); Kaasik and Lee (2004); Yin et al. (2007)

pathology of addiction (Spanagel et al., 2005).

Metabolic control of circadian rhythms

From the evidence summarised above it seems clear that major aspects of metabolism are under circadian control. However, communication between metabolism and the clock is not linear. Instead, there seems to be a bidirectional relationship where metabolic cues feedback on the regulation of circadian timing. Evidence from both human and animal studies as well as possible molecular mechanisms underlying such metabolic clock control are discussed in the following paragraphs.

The prevalence of obesity has been steadily increasing in the last decades, as has sleep curtailment (see above). Obese people tend to show changes in sleep architecture indicative of circadian clock disturbances (Resnick et al., 2003). For sleep disorders it is sometimes difficult to differentiate between altered sleep homeostasis and changes in the circadian control of sleep, but altered daily rhythms of humoral parameters in obese people strongly suggest an involvement of the circadian timing system. Obese people show severely blunted to absent rhythms in glucose tolerance over the course of the day (Van Cauter et al., 1997). Additionally, the diurnal secretion rhythms of ghrelin are severely altered in obese people compared with lean subjects (Yildiz et al., 2004). However, how the circadian deregulation of such parameters influences the development of the disease remains to be shown.

In rodents obesity can be either induced by high fat feeding (HFF) or by genetic manipulation resulting in an obese phenotype. Both approaches indicate that obesity impairs the regulation of circadian clocks. Feeding mice with a high fat chow lengthens the period of circadian locomotor activity and changes circadian feeding patterns. Moreover, HFF affects clock gene rhythms in the liver as well as the circadian pattern of leptin, insulin and glucocorticoid levels in the blood (Kohsaka et al., 2007). Interestingly, not only feeding but also the complete withdrawal of food during fasting changes clock gene expression in peripheral tissues (Kawamoto et al., 2006). Obesity-inducing genetic mutations also lead to severe impairments of circadian rhythmicity. Mice defi-

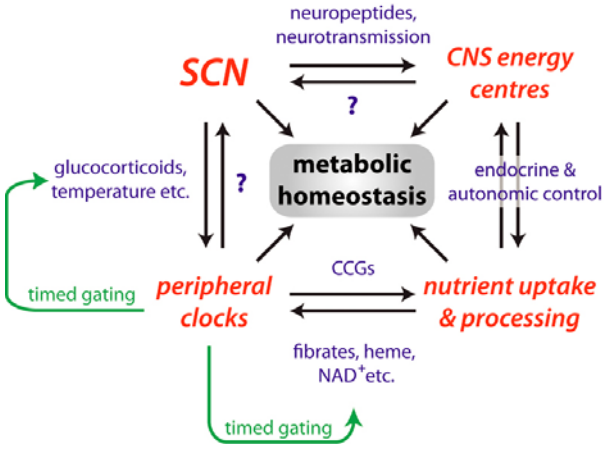

Fig. 1. Interaction of circadian and metabolic regulatory centres in the control of metabolic homeostasis. Central and peripheral circadian and metabolic centres (red) interact via humoral and neuronal factors (blue). Clock-controlled gating of the sensitivity of the target tissue for external stimuli (green) minimises the effect of noise and sporadic signalling events, promoting robust coupling between different oscillatory functions. For more details see text.

cient of the adipocyte satiety signal leptin (*ob*/*ob*) show a clear obese phenotype correlated with dampened locomotor activity rhythms and disrupted sleep architecture (Laposky et al., 2006). In another mouse model of diabetic obesity (*KK-A^y* mice) it was shown that the circadian clock is impaired at the molecular level. Clock gene rhythms in liver and white adipose tissue of *KK-A^y* mice are severely attenuated (Ando et al., 2005). One study compared the effects of HFF and genetically induced obesity on clock gene expression and showed that clock gene rhythms in the CNS are equally disturbed in all obesity models (Kaneko et al., 2009). Taken together, human and mouse studies clearly suggest that obesity alters circadian clock regulation at the behavioural, physiological and molecular level.

The fact that feeding time can act as a *Zeitgeber* and change the phase of clock genes in peripheral organs, and most prominently in the liver, has long been known. Mice or rats that are subjected to a restricted feeding (RF) schedule, wherein food is only given for some hours during their normal sleeping time, show a complete uncoupling of peripheral clocks from the master pacemaker in the SCN: while clock gene expression in peripheral organs is entrained by the feeding schedule, the SCN retains its synchrony with the external light/dark cycle (Damiola et al., 2000). It remains unclear how the food-induced entrainment of peripheral clocks functions at the molecular level. Injection of the synthetic glucocorticoid dexamethasone can phase shift clock genes in the liver in a time-dependent manner (Balsalobre et al., 2000). Deletion of the glucocorticoid receptor in the liver, however, does not prevent entrainment of the liver clock after RF (Le Minh et al., 2001). Of course, nutrient components (carbohydrates, lipids and amino acids) themselves could affect the clock, and recent data suggest that metabolic cues might act on clock function through nuclear hormone receptors (NRs), some of which directly participate in the regulation of the circadian machinery. As sensors of dietary lipids, vitamins and lipophilic hormones, NRs are prime candidates for linking metabolism to the circadian clock. Indeed, about 50% of NRs show diurnal variations in expression and, hence, are themselves regulated by the circadian clock (Yang et al., 2006). Importantly, the two orphan nuclear receptors REV-ERBα (NR1D1) and RORα (RORA) together represent one of the transcriptional feedback loops that underlie circadian regulation at the cellular level (Preitner et al., 2002; Sato et al., 2004). As *Rev-erbα* is required for adipogenesis and *Rorα* is important for lipid homeostasis, these two NRs might directly link metabolism to circadian clock function (Lau et al., 2004; Wang and Lazar, 2008). Peroxisome proliferator-activated receptor α (PPARA) is another important NR, a sensor for fatty acids and is involved in the regulation of energy metabolism (Lefebvre et al., 2006). Fibrates are known PPARA agonists that are used to treat symptoms of obesity and metabolic syndrome. *Rev-erbα* is a target of PPARA and fibrate treatment induces *Rev-erbα* expression via binding of PPARA to PPARA response elements in the *Rev-erbα* promoter (Gervois et al., 1999). Interestingly, PPARA is necessary for normal circadian clock gene expression in peripheral tissues such as the liver (Canaple et al., 2006). PPARA regulates *Bmal1* expression via a PPAR response element in the *Bmal1* promoter and is reciprocally regulated by CLOCK/BMAL1 (see Table 1). *Ppara* expression is phase shifted in response to a RF schedule and *Ppara knockout* mice show altered phase shifts in brown adipose tissue and heart after RF, implying that this NR might be one of the molecular mediators of food entrainment (Goh et al., 2007). Similar functions as for PPARA have also been proposed for its close relative PPARG (Fontaine et al., 2003). A known PPAR-interacting factor is PGC-1α (PPARGC1A), a transcriptional coactivator that plays a critical role in the maintenance of energy metabolism in a number of tissues. PGC-1α is involved in thermogenesis in brown adipose tissue and in the regulation of gluconeogenesis in the liver (Lin et al., 2005). Besides metabolic abnormalities *Pgc-1α* deficient mice display changes in important circadian parameters with a lengthened period of locomotor activity and perturbed clock gene expression in different tissues. PGC-1α induces the clock gene *Bmal1* via coactivation of RORs. Interestingly, and similar to *Ppara* deficient mice, food entrainment of the periphery is disrupted after a RF schedule in *Pgc-1α* deficient mice (Liu et al., 2007), implicating that PGC-1α might be involved in RF induced clock resetting.

Besides the involvement of NRs and NR-interacting factors in transmitting food signals to the molecular clock, clock genes themselves can be sensors for the metabolic state of the cell. Carbon monoxide (CO) inhibits the DNA binding of NPAS2 by favouring inactive BMAL1 homodimerization instead of active NPAS2/BMAL1 heterodimerization (Dioum et al., 2002). Along this line, NPAS2 and REV-ERBα have both been shown to act as heme sensors, where heme binding controls the DNA binding activity of these two core clock components (Kaasik and Lee, 2004; Yin et al., 2007). However, heme not only controls clock function, but the regulation of the rate limiting enzyme of heme biosynthesis, ALAS1, by the clock, reciprocally impacts on heme production itself (Kaasik and Lee, 2004). Additional evidence for clock genes being sensors of the cellular metabolic state comes from studies showing that the DNA binding activity of CLOCK/BMAL1 heterodimers is dependent on the redox state of the cell (Rutter et al., 2001). The molecular cascade underlying this phenomenon involves the rate limiting enzyme in the NAD synthesis, NAMPT, and the histone deacetylase SIRT1, a suppressor of CLOCK/BMAL1-mediated transcription (Nakahata et al., 2009; Ramsey et al., 2009). Interestingly - and similar to what was shown for heme - *Nampt* transcription itself is clock controlled, providing a mechanism for a gating of the sensitivity of the clock that allows a time-dependent response of peripheral circadian clocks to redox state signalling (Fig. 1).

CONCLUSION

In summary, it has become increasingly clear that circadian and metabolic regulation is tightly interlocked at both physiological and molecular levels (Fig. 1). The expression or enzymatic activity for key regulators of metabolic homeostasis show circadian rhythms, while metabolic sensors such as NRs and redox equivalents can directly feed-back on the transcriptional processes underlying the generation of circadian rhythmicity. These findings all point at a critical role for the circadian clock in the optimisation of energy expenditure and, thus, the increase of fitness under highly selective natural conditions. Such strict selective pressure does not exist under normal laboratory conditions. This might underlie the surprising fact that the evolutionary advantage of having a functional circadian timekeeping system has so far, at least in mammals, not been experimentally proven. Informative studies have been conducted in simpler species such as plants (Michael et al., 2003) and cyanobacteria. Mixing cultures of different strains of *Synechococcus elongates* shows that only those bacteria with an internal circadian period which closely matches the external light/dark cycle survive (Woelfle et al., 2004). Short life spans have been reported for *Bmal1*-deficient mice, but not for other clock mutants, indicating that this phenotype might represent a pleiotropic function of *Bmal1* besides its regulation of circadian timing (Kondratov et al., 2006).

Our modern lifestyle imposes new ways of pressure on the

functionality of metabolism and clocks. Strictly timed (or even shift) work schedules and transcontinental travel together with the omnipresence of artificial lighting represent strong challenges for a primarily light-driven system such as the circadian clock. The consequence is what has been coined as *social jetlag*, a chronic misalignment of internal and external rhythms (Wittmann et al., 2006). Social jetlag - just like its air travel-associated brother - might have strong implications for the functionality of metabolism, but also for immunity and cognitive performance.

The bilateral relationship of metabolic homeostasis and circadian clock function outlined above makes both systems vulnerable to factors impinging on the other. At the same time, it also offers new roads for the treatment of diseases associated with either of both processes. Time-scheduled and nutrient-controlled food uptake can influence clock phase and stability and, thus, might help to alleviate disease symptoms associated with circadian misalignment such as sleep disruption, jetlag and various neuropsychiatric disorders (Oster and Foster, 2008). Likewise, resetting clock phase or strengthening internal synchronization, e.g. by timed light exposure or scheduled sleep/wake times, might affect metabolic pathologies such as obesity, diabetes and night eating syndrome (Levi and Schibler, 2007). Given the increasing prevalence and fatality rates of obesity-associated disorders, tackling the circadian clock has the potential to become an important instrument in fighting obesity as a major plague of the industrialised world.

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